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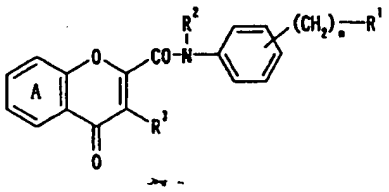
(54) Title: CHROMONE DERIVATIVES, PROCESS FOR THE PREPARATION OF THE SAME AND USES THEREOF

(54) 発明の名称: クロモン誘導体、その製造法及び用途

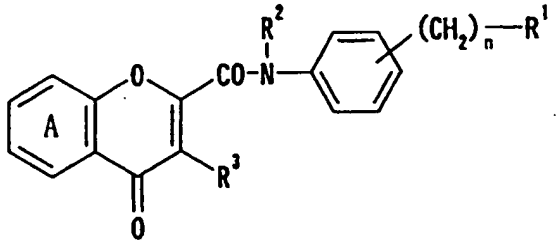


(I)

(57) Abstract: Chromone derivatives represented by general formula (I) or salts thereof; a process for the preparation thereof; and preventive or therapeutic agents for bone diseases, cartilage diseases or fracture, containing the derivatives or the salts. In said formula (I) A is an optionally substituted benzene ring; R^1 is an optionally substituted nonaromatic heterocyclic group; R^2 is hydrogen or hydrocarbyl; R^3 is hydrogen, hydrocarbyl, or halogeno; and n is an integer of 0 to 3.

(57) 要約:

式



[式中、環Aは置換基を有していてもよいベンゼン環を、R^1は置換基を有していてもよい非芳香族複素環基を、R^2は水素原子または炭化水素基を、R^3は水素原子、炭化水素基またはハロゲンを、nは0～3の整数を、それぞれ示す] で表されるクロモン誘導体またはその塩、その製造法および前記クロモン誘導体またはその塩を含有してなる骨疾患、軟骨疾患、骨折の予防・治療剤を提供する。

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DESCRIPTION

CHROMONE DERIVATIVES, AND PREPARATION PROCESS AND USES THEREFOR

Technical Field

The present invention relates to chromone derivatives with an osteogenesis accelerating effect, and to a preparation process and uses therefor.

Background Art

Osteoporosis is a pathological condition in which quantitative bone loss exceeds a certain level, resulting in various symptoms and risks. The major symptoms are fractures of the spinal kyphosis and dorsolumbar bone, as well as the vertebral body, femoral neck, lower radius, vomer, upper humerus, etc. In bone tissue, osteogenesis and osteoclasis by resorption are constantly in repetitive progress while maintaining a balance, with osteoblasts playing the central role in osteogenesis and osteoclasts in bone resorption. When this balance between osteogenesis and osteoclasis by resorption is broken and bone resorption becomes dominant over bone formation, the quantitative bone loss characteristic of osteoporosis results.

Estrogen agents, calcitonin, bisphosphonates and the like have been the major bone resorption inhibitors used as prophylactic drugs against osteoporosis. However, administration of these bone resorption inhibitors is limited to specific cases, while their effects are often unreliable and insufficient. It has therefore been a desire to develop osteogenesis (bone formation) accelerators which actively increase bone volume which has been reduced, as prophylactic drugs against osteoporosis.

Japanese Unexamined Patent Publication HEI No. 7-291983 discloses b nzopyran derivatives having an osteogenesis

accelerating effect.

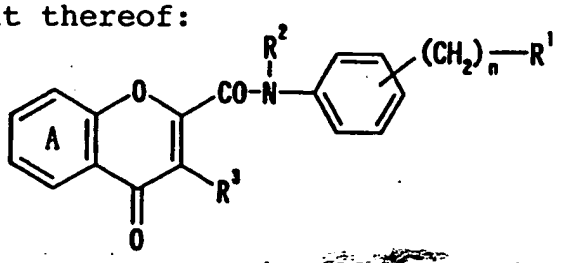
Disclosure of the Invention

The present invention provides chromone derivatives with a markedly superior osteogenesis accelerating effect, a preparation process therefor, and osteogenesis accelerators comprising them as active ingredients.

Upon carrying out diligent research directed toward developing compounds with osteogenesis accelerating effects, the present inventors found that chromone derivatives having a group to which a nonaromatic heterocyclic group is bonded exhibit a markedly superior osteogenesis accelerating effect, and completed the present invention upon further research based on this knowledge.

Specifically, the present invention provides

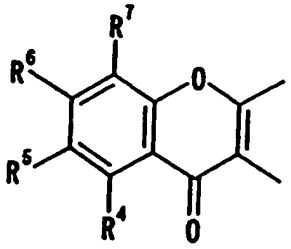
(1) a chromone derivative represented by the following formula, or a salt thereof:



where ring A represents an optionally substituted benzene ring, R^1 represents an optionally substituted nonaromatic heterocyclic group, R^2 represents a hydrogen atom or hydrocarbon group, R^3 represents a hydrogen atom, hydrocarbon group or halogen, and n is an integer of 0 to 3,

(2) a compound according to (1) above or a salt thereof, wherein ring A is a benzene ring optionally substituted with 1 to 3 substituents selected from among hydroxy, acyloxy, mercapto, halogens, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} alkylthio and alkylenedioxy represented by the formula $-O-(CH_2)_m-O-$ (where m is an integer of 1 to 4), R^2 is hydrogen or C_{1-6} alkyl and R^3 is hydrogen,

(3) a compound according to (1) above or a salt thereof, wherein the partial structure including ring A is represented

by the formula: 

where R^4 represents hydrogen or hydroxyl, and R^5-R^7 each represent hydrogen, a halogen, C_{1-10} alkyl or C_{1-10} alkoxy and are either the same or different,
R^2 is hydrogen or a C_{1-6} alkyl and R^3 is hydrogen,

(4) a compound according to (1) above or a salt thereof, wherein the nonaromatic heterocyclic group for the optionally substituted nonaromatic group represented by R^1 is a 5- to 7-membered nonaromatic heterocyclic group containing from 1 to 4 hetero atoms selected from among nitrogen, sulfur and oxygen,

(5) a compound according to (4) above or a salt thereof, wherein the 5- to 7-membered nonaromatic heterocyclic group for the optionally substituted 5- to 7-membered nonaromatic heterocyclic group is a 5- to 7-membered nonaromatic heterocyclic group containing at least one nitrogen atom,

(6) a compound according to (5) above or a salt thereof, wherein the 5- to 7-membered nonaromatic heterocyclic group for the optionally substituted 5- to 7-membered nonaromatic heterocyclic group is pyrrolidine, imidazolidine, thiazolidine, isothiazolidine, oxazolidine, oxadiazolidine, piperidine, piperazine, thiomorpholine or morpholine,

(7) a compound according to (1) above or a salt thereof, wherein the optionally substituted nonaromatic heterocyclic group represented by R^1 has 1 to 4 substituents selected from among halogen, hydroxy, oxo, C_{1-10} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, amino, mono- or di- C_{1-6} alkylamino, C_{1-6} alkylsulfonyl, carboxy, C_{1-6} alkoxy-carbonyl and phosphono groups,

(8) a compound according to (3) above or a salt thereof, wherein R^2 is hydrogen and R^4 is hydroxyl,

(9) a compound according to (3) above or a salt thereof, wherein R^2 and R^4 are both hydrogen,

(10) a prodrug of a compound according to (1) above,

(11) N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,4-dioxooxazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

5,7-dihydroxy-N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-5-hydroxy-7-methoxy-4-oxo-4H-1-benzopyran-2-carboxamide,

5,7-dihydroxy-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

5-hydroxy-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2-oxazolidon-3-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,6-dioxo-1-piperidinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

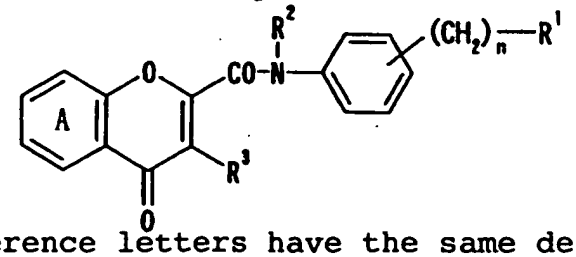
N-[4-[(2,4-dioxooxazolidin-5-yl)methyl]phenyl]-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide,

5-hydroxy-N-methyl-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide, or

4-oxo-N-[4-[(4-oxo-1-piperidinyl)methyl]phenyl]-4H-1-benzopyran-2-carboxamide,

or a salt thereof,

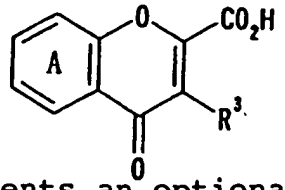
(12) a process for preparation of a chromone derivative represented by the following formula, or a salt thereof:



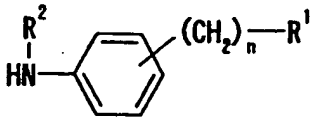
where the reference letters have the same definitions explained above,

characterized by reacting a compound represented by the following formula, a derivative thereof reactive at the

carboxyl group, or a salt thereof:



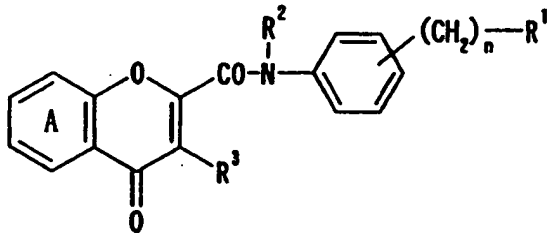
where ring A represents an optionally substituted benzene ring and R^3 represents a hydrogen atom, hydrocarbon group or halogen, with a compound represented by the following formula, a derivative thereof reactive at the amino group, or a salt thereof:



where R^1 represents an optionally substituted nonaromatic heterocyclic group, R^2 represents a hydrogen atom or hydrocarbon group and n is an integer of 0 to 3,

(13) 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid, 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid or 5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid, or a salt thereof,

(14) a pharmaceutical composition comprising a chromone derivative represented by the following formula, or a salt thereof:



where ring A represents an optionally substituted benzene ring, R^1 represents an optionally substituted nonaromatic heterocyclic group, R^2 represents a hydrogen atom or hydrocarbon group, R^3 represents a hydrogen atom, hydrocarbon group or halogen, and n is an integer of 0 to 3,

(15) a pharmaceutical composition according to (14) above, which is an osteogenesis accelerator,

(16) a pharmaceutical composition according to (14) above, which is a prophylactic or tr atment agent for bone disease,

(17) a pharmaceutical composition according to (14) above, which is a prophylactic or treatment agent for bone fracture,

(18) a pharmaceutical composition according to (14) above, which is a prophylactic or treatment agent for cartilage diseases,

(19) a pharmaceutical composition comprising a prodrug according to (10) above,

(20) an osteogenesis accelerating method characterized by administering a compound according to (1) above or a salt thereof, and

(21) the use of a compound according to (1) above or a salt thereof for preparation of an osteogenesis accelerator.

Best Mode for Carrying Out the Invention

As substituents for the optionally substituted benzene rings represented by ring A in the formulas shown above there may be used, for example, halogen atoms, nitro, optionally substituted alkyl groups, optionally substituted hydroxy groups, optionally substituted mercapto groups, optionally substituted amino groups, acyl, mono- or di- alkoxyphosphoryl groups, phosphono, optionally substituted aryl groups, optionally substituted aralkyl groups and optionally substituted aromatic heterocyclic groups, where 1 to 4 and preferably 1 to 3 of these substituents, either the same or different, may be substituted on the benzene ring.

As "halogen atoms" there may be used, for example, fluorine, chlorine, bromine, iodine and the like.

As alkyl groups of the "optionally substituted alkyl groups" there may be preferably used alkyl groups of 1-10 carbons (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl or decyl) and cycloalkyl groups of 3-7 carbons (for example, cyclopropyl, cyclobutyl, cyclohexyl or cycloheptyl), which may have 1 to 3 substituents such as, for example, halogen atoms (fluorine, chlorine, bromine,

iodine, etc.), hydroxy groups, alkoxy groups of 1-6 carbons (methoxy, ethoxy, propoxy, butoxy, hexyloxy, etc.), mono- or di- (C_{1-6} alkoxy)phosphoryl groups (methoxyphosphoryl, ethoxyphosphoryl, dimethoxyphosphoryl, diethoxyphosphoryl, etc.), phosphono, and the like.

As specific examples of substituted alkyl groups there may be mentioned trifluoromethyl, trifluoroethyl, trichloromethyl, hydroxymethyl, 2-hydroxyethyl, 1-methoxyethyl, 2-methoxyethyl, 2,2-diethoxyethyl, 2-diethoxyphosphorylethyl and phosphonomethyl.

As the hydroxy groups for the "optionally substituted hydroxy groups" there may be used, for example, alkoxy groups, alkenyloxy groups, aralkyloxy groups, acyloxy groups, aryloxy groups and the like. As the "alkoxy groups" there may be used preferably alkoxy groups of 1-10 carbons (for example, methoxy, ethoxy, propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, heptyloxy or nonyloxy) and cycloalkoxy groups of 4-6 carbons (for example, cyclobutoxy, cyclopentoxy or cyclohexyloxy). As the "alkenyloxy groups" there may be used preferably alkenyloxy groups of 2-10 carbons, for example, allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy or 2-cyclohexenylmethoxy. As the "aralkyloxy groups" there may be used preferably aralkyloxy groups of 7-19 carbons, and more preferably C_{6-14} aryl-C_{1-4} alkyloxy groups (for example, benzyloxy, phenethyloxy, etc). As the "acyloxy groups" there may be used, for example, alkanoyloxy groups, carbamoyloxy groups and alkoxycarbonyloxy groups (preferably, C_{1-10} alkoxycarbonyloxy). As the "acyloxy groups" there may be used preferably alkanoyloxy groups, for example, alkanoyloxy groups of 2-10 carbons (for example, acetyloxy, propionyloxy, n-butyryloxy, i-butyryloxy, hexanoyloxy, etc.). "Carbamoyloxy groups" include not only carbamoyloxy but also substituted carbamoyloxy groups, for example, carbamoyloxy groups substitut d with 1-2 alkyl groups. As alkyl groups of the carbamoyloxy groups substituted with 1-2 alkyl groups there

may be used alkyl groups of 1-10 carbons (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl or decyl) or cycloalkyl groups of 3-7 carbons (for example, cyclopropyl, cyclobutyl, cyclohexyl or cycloheptyl), and preferably alkyl groups of 1-6 carbons. As preferred carbamoyloxy groups there may be mentioned carbamoyloxy, methylcarbamoyloxy, dimethylcarbamoyloxy, ethylcarbamoyloxy, diethylcarbamoyloxy and the like. As the "aryloxy groups" there may be used preferably aryloxy groups of 6-14 carbons (for example, phenoxy, biphenyloxy, etc.). These groups may also have 1 to 3 substituents from among, for example, the aforementioned halogen, hydroxy, C_{1-6} alkoxy, mono- or di-(C_{1-6} alkoxy)phosphoryl and phosphono groups. As specific examples of substituted hydroxy groups there may be mentioned trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-methoxyethoxy, 4-chlorobenzyloxy, 2-(3,4-dimethoxyphenyl)ethoxy, methoxy, methylenedioxy, acetyloxy, n-butyryloxy, i-butyryloxy and diethylcarbamoyloxy.

As the substituted mercapto groups for the "optionally substituted mercapto groups" there may be mentioned mercapto groups substituted with the same groups as the substituents for the "optionally substituted hydroxy groups" mentioned above, and preferred examples are alkylthio groups, aralkylthio groups, acylthio groups and the like. As the "alkylthio groups" there may be used preferably alkylthio groups of 1-10 carbons (for example, methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, nonylthio, etc.) and cycloalkylthio groups of 4-6 carbons (for example, cyclobutylthio, cyclopentylthio, cyclohexylthio, etc.). As the "aralkylthio groups" there may be used preferably aralkylthio groups of 7-19 carbons, and more preferably C_{6-14} aryl-C_{1-4} alkylthio groups, for example, benzylthio, phenethylthio and the like. As the "acylthio groups" there may be used preferably alkanoylthio groups, for

example, alkanoylthio groups of 2-10 carbons (for example, acetylthio, propionylthio, n-butyrylthio, hexanoylthio, etc.). These groups may also have 1 to 3 substituents from among, for example, the aforementioned halogen, hydroxy, C_{1-6} alkoxy, mono- or di-(C_{1-6} alkoxy)phosphoryl and phosphono groups. As specific examples of substituted thio groups there may be mentioned, for example, trifluoromethylthio, 2,2,2-trifluoroethylthio, 2-methoxyethylthio, 4-chlorobenzylthio, 3,4-dichlorobenzylthio, 4-fluorobenzylthio, 2-(3,4-dimethoxyphenyl)ethylthio and the like.

As substituents on the substituted amino groups of the "optionally substituted amino groups" there may be used one or more of the aforementioned alkyl groups of 1-10 carbons, alkenyl groups of 2-10 carbons (for example, allyl, vinyl, 2-penten-1-yl, 3-penten-1-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-cyclohexenyl, 2-cyclopentenyl, 2-methyl-2-propen-1-yl, 3-methyl-2-buten-1-yl, etc.), aryl groups of 6-14 carbons or aralkyl groups of 7-19 carbons, which may be the same or different, and these substituents may be in turn substituted with the aforementioned halogen, hydroxy, C_{1-6} alkoxy, mono- or di-(C_{1-6} alkoxy)phosphoryl and phosphono groups. As specific examples of substituted amino groups there may be mentioned methylamino, dimethylamino, ethylamino, diethylamino, dibutylamino, diallylamino, cyclohexylamino, phenylamino, N-methyl-N-phenylamino, N-methyl-N-(4-chlorobenzyl)amino and N,N-di-(2-methoxyethyl)amino.

As the "acyl groups" there may be used organic carboxylic acyl groups, sulfonic acyl groups having hydrocarbon groups of 1-6 carbons (for example, methyl, ethyl, n-propyl, hexyl, phenyl, etc.), carbamoyl groups and the like. As the "organic carboxylic acyl groups" there may be used, for example, formyl, alkyl-carbonyl groups of 1-10 carbons (for example, acetyl, propionyl, butyryl, valeryl, pivaloyl, hexanoyl, octanoyl, cyclobutanecarbonyl, cyclohexanecarbonyl, cycloheptanecarbonyl, etc.), alkenyl-carbonyl groups of 2-10 carbons (for example,

crotonyl, 2-cyclohexenecarbonyl, etc.), aryl-carbonyl groups of 6-14 carbons (for example, benzoyl, etc.), aralkyl-carbonyl groups of 7-19 carbons (for example, benzylcarbonyl, benzhydrylcarbonyl, etc.), 5- or 6-membered aromatic heterocyclic carbonyl groups (for example, nicotinoyl, 4-thiazolylcarbonyl, etc.) and 5- or 6-membered aromatic heterocyclic acetyl groups (for example, 3-pyridylacetyl, 4-thiazolylacetyl, etc.). As the "sulfonic acyl groups having hydrocarbon groups of 1-6 carbons" there may be used for example, C_{1-6} alkanesulfonyl groups such as methanesulfonyl, ethanesulfonyl and the like. These groups may also have 1 to 3 substituents from among, for example, the aforementioned halogen, hydroxy, C_{1-6} alkoxy and amino groups. As specific examples of acyl groups there may be mentioned trifluoroacetyl, trichloroacetyl, 4-methoxybutyryl, 3-cyclohexyloxypropionyl, 4-chlorobenzoyl, 3,4-dimethoxybenzoyl and the like. "Carbamoyl groups include not only carbamoyl but also substituted carbamoyl groups, for example, carbamoyl groups substituted with 1-2 alkyl groups. As alkyl groups of the carbamoyl groups substituted with 1-2 alkyl groups there may be used alkyl groups of 1-10 carbons (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl or decyl) or cycloalkyl groups of 3-7 carbons (for example, cyclopropyl, cyclobutyl, cyclohexyl or cycloheptyl), with alkyl groups of 1-6 carbons being preferred. As preferred carbamoyl groups there may be mentioned carbamoyl, methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl and ethylmethylcarbamoyl.

As the "mono- or di-alkoxyphosphoryl groups" there may be used mono-C_{1-6} alkoxyphosphoryl groups such as methoxyphosphoryl, ethoxyphosphoryl, propoxyphosphoryl, isopropoxyphosphoryl, butoxyphosphoryl, pentyloxyphosphoryl and hexyloxyphosphoryl, or di-C_{1-6} alkoxyphosphoryl groups such as dimethoxyphosphoryl, diethoxyphosphoryl,

dipropoxyphosphoryl, diisopropoxyphosphoryl, dibutoxyphosphoryl, dipentyloxyphosphoryl and dihexyloxyphosphoryl. Preferred for use are di-C_{1-6} alkoxy groups such as dimethoxyphosphoryl, diethoxyphosphoryl, dipropoxyphosphoryl diisopropoxyphosphoryl, ethylenedioxyphosphoryl, dibutoxyphosphoryl and the like.

As aryl groups for the "optionally substituted aryl groups" there may be used preferably aryl groups of 6-14 carbons such as phenyl, naphthyl and anthryl, and these may also have 1 to 3 substituents from among, for example, the aforementioned C_{1-10} alkyl, halogen, hydroxy and C_{1-6} alkoxy groups. As specific examples of substituted aryl groups there may be mentioned 4-chlorophenyl, 3,4-dimethoxyphenyl, 4-cyclohexylphenyl and 5,6,7,8-tetrahydro-2-naphthyl.

As aralkyl groups for the "optionally substituted aralkyl groups" there may be used preferably aralkyl groups of 7-19 carbons such as benzyl, naphthylethyl and trityl, and their aromatic rings may be substituted with 1 to 3 substituents from among the aforementioned C_{1-10} alkyl, halogen, hydroxy and C_{1-6} alkoxy groups. As specific examples of substituted aralkyl groups there may be mentioned 4-chlorobenzyl, 3,4-dimethoxybenzyl, 4-cyclohexylbenzyl and 5,6,7,8-tetrahydro-2-napthylethyl.

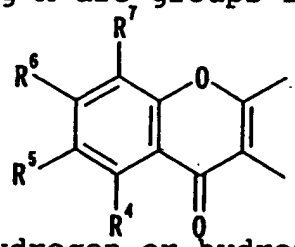
As aromatic heterocyclic groups of the "optionally substituted aromatic heterocyclic groups" there may be used preferably 5- or 6-membered aromatic heterocyclic groups with 1 to 4 nitrogen, oxygen and/or sulfur atoms, such as furyl, thienyl, imidazolyl, thiazolyl, oxazolyl and thiadiazolyl, and these groups may be substituted with 1 to 3 substituents from among the aforementioned C_{1-10} alkyl, halogen, hydroxy and C_{1-6} alkoxy groups.

When two alkyl groups are adjacently substituted on the benzene ring A, they may be linked together to form an alkylene group represented by the formula: $-(CH_2)_L-$ (where L is an integer of 3 to 5) (for xample, trimethylene,

tetramethylene, pentamethylene, etc.), and when two alkoxy groups are adjacently substituted they may form an alkylenedioxy group represented by the formula: $-O-(CH_2)_m-O-$ (where m is an integer of 1 to 4) (for example, methylenedioxy, ethylenedioxy, trimethylenedioxy, etc.). In such cases, a 5- to 8-membered ring will be formed with the carbon atoms of the benzene ring.

As preferred substituents on ring A there may be mentioned, for example, hydroxy groups, C_{2-10} alkanoyloxy groups, carbamoyloxy groups substituted with 1 or 2 C_{1-10} alkyl groups, mercapto groups, halogen atoms, C_{1-10} alkyl groups, C_{1-10} alkylthio groups and alkylenedioxy groups represented by the formula: $-O-(CH_2)_m-O-$ (where m is an integer of 1 to 4), with the number of substituents preferably being 1 to 3.

Preferred as ring A are groups represented by the formula:



where R^4 represents hydrogen or hydroxyl, and R^5-R^7 each represent hydrogen, a halogen, C_{1-10} alkyl or C_{1-10} alkoxy and are either the same or different.

Hydrogen or hydroxyl is preferred as R^4, with hydroxyl being particularly preferred.

As nonaromatic heterocyclic rings of the optionally substituted nonaromatic heterocyclic group represented by R^1 in the above formula there may be mentioned 3- to 8-membered (preferably 5- to 7-membered) nonaromatic heterocyclic rings containing from 1 to 4 hetero atoms selected from among nitrogen, sulfur and oxygen atoms. That is, they are preferably nonaromatic heterocyclic rings wherein the hetero atoms are selected from among nitrogen, sulfur and oxygen atoms, and more preferably 3- to 8-membered nonaromatic heterocyclic rings wherein the hetero atoms are selected from among nitrogen, sulfur and oxygen atoms. As examples there

may be mentioned oxirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, thiolane, piperidine, tetrahydropyran, morpholine, thiomorpholine, piperazine, homopiperidine, pyrroline, imidazolidine, thiazoline, isothiazoline, thiazolidine, isothiazolidine, imidazoline, oxazoline, oxazolidine, oxadiazolidine, oxathiazolidine, dithiazolidine and thiadiazolidine. Among these, 5- to 7-membered nonaromatic heterocyclic rings containing at least one nitrogen atom are preferred, with pyrrolidine, imidazolidine, thiazolidine, isothiazolidine, oxazolidine, oxadiazolidine, piperidine, piperazine, thiomorpholine and morpholine being particularly preferred.

As substituents for the optionally substituted nonaromatic heterocyclic group in the above formula there may be mentioned, for example, (i) halogen atoms (fluorine, chlorine, bromine, iodine, etc.), (ii) hydroxy or oxo, (iii) C_{1-10} alkyl (methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), (iv) C_{1-6} alkoxy (methoxy, ethoxy, propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, etc.), (v) C_{1-6} acyl (acetyl, propionyl, etc.), (vi) C_{1-6} amino optionally substituted with C_{1-6} alkyl (amino, methylamino, ethylamino, dimethylamino, diethylamino, dipropylamino, etc.), (vii) C_{1-6} alkylsulfonyl, (viii) carboxy, (ix) C_{1-6} alkoxy-carbonyl (methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), (x) phosphono and the like. The number of substituent may be from 1 to 4.

As specific examples of optionally substituted nonaromatic heterocyclic rings there may be mentioned nonaromatic heterocyclic groups such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidyl, 4-oxopiperidyl, pyrrolinyl, imidazolidinyl, 4-formylpiperazinyl, 4-methanesulfonylpiperazinyl, 3-hydroxypyrrolidinyl, 2,4-

dioxothiazolidin-5-yl, 2,4-dioxothiazolidin-3-yl, hydantoin-3-yl, glutarimid-4-yl, 1-methylhydantoin-3-yl, succinimide, 2-oxazolidon-3-yl, 2,4-dioxooxazolidin-5-yl, 2,4-dioxooxazolidin-3-yl, 1,1-dioxotetrahydro-2H-1-isothiazol-2-yl and 3,5-dioxo-1,2,4-oxadiazolidin-2-yl. These nonaromatic heterocyclic groups may be condensed with a benzene ring, a 6-membered ring containing up to 2 nitrogen atoms or a 5-membered ring containing one sulfur atom. As specific examples of condensed nonaromatic heterocyclic groups there may be mentioned chromanyl, isochromanyl, indolinyl, isoindolinyl, thiochromanyl, isothiochromanyl and the like.

As hydrocarbon groups represented by R^2 and R^3 in the above formula there may be used the same alkyl groups as mentioned above (preferably alkyl groups of 1-10 carbons, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.), alkenyl groups (preferably alkenyl groups of 2-10 carbons, for example, vinyl, allyl, isopropenyl, 2-methylallyl, 1-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-ethyl-1-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, etc.), alkynyl groups (preferably alkynyl groups of 2-10 carbons, for example, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, etc.), cycloalkyl groups (preferably cycloalkyl groups of 3-9 carbons, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, etc.), cycloalkenyl groups (preferably cycloalkenyl groups of 3-6 carbons, for example, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl, 3-cyclohexen-1-yl, 1-cyclobuten-1-yl, 1-cyclopenten-1-yl, etc.), aryl groups (preferably aryl groups of 6-14 carbons, for example, phenyl, 1-naphthyl, 2-naphthyl, anthryl, phenanthryl,

acenaphthylenyl, etc.), aralkyl groups (preferably aralkyl groups of 7-19 carbons, for example, benzyl, phenethyl, etc.), and the like.

Preferred as the aforementioned hydrocarbon groups are linear or branched C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl and hexyl. Of these, C_{1-4} alkyl groups are especially preferred.

Preferred as R^2 are hydrogen and C_{1-6} alkyl groups, with hydrogen being particularly preferred.

As halogens for R^3 there may be mentioned the same halogen atoms as above.

Hydrogen is particularly preferred as R^3.

In the formula, n represents an integer of 0 to 3 but is preferably 1 or 2.

The following may be mentioned as particularly preferred examples of these compounds.

N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,4-dioxooxazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

5,7-dihydroxy-N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-5-hydroxy-7-methoxy-4-oxo-4H-1-benzopyran-2-carboxamide,

5,7-dihydroxy-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

5-hydroxy-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2-oxazolidon-3-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,6-dioxo-1-piperidinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

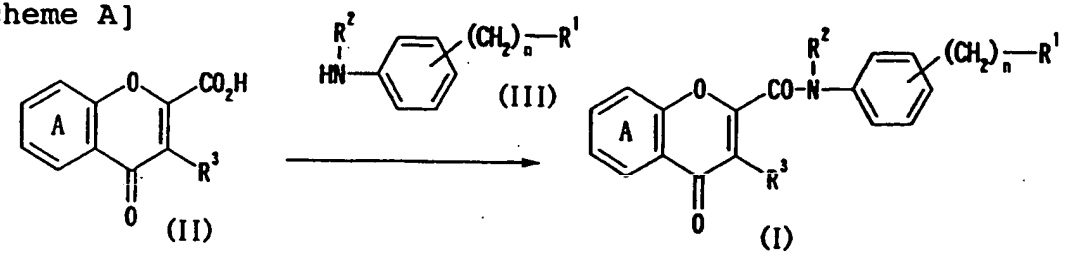
5-hydroxy-N-[4-[(2,4-dioxooxazolidin-5-yl)methyl]ph nyl]-4-oxo-4H-1-benzopyran-2-carboxamide,
5-hydroxy-N-methyl-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide, and
4-oxo-N-[4-[(4-oxo-1-piperidinyl)methyl]phenyl]-4H-1-benzopyran-2-carboxamide,
as well as salts thereof.

As salts of these compounds there are preferred pharmaceutically acceptable salts, and for example, there may be mentioned salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids. As preferred examples of salts with inorganic bases there may be mentioned alkali metal salts such as sodium salts and potassium salts, alkaline earth metal salts such as calcium salts and magnesium salts, and aluminum salts, ammonium salts and the like. As preferred examples of salts with organic bases there may be mentioned salts with, for example, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, dicyclohexylamine and N,N'-dibenzylethylenediamine. As preferred examples of salts with inorganic acids there may be mentioned salts with, for example, hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid and the like. As preferred examples of salts with organic acids there may be mentioned salts with, for example, formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. As preferred examples of salts with basic amino acids there may be mentioned salts with, for example, arginine, lysine and ornithine, and as preferred examples of salts with acidic amino acids there may be mentioned salts with, for xample, aspartic acid and glutamic acid.

The present invention provides a process for preparation of compounds represented by formula (I) and salts thereof.

The compounds and their salts represented by formula (I) [hereunder referred to collectively as "Compound (I)"] are prepared, for example, by the following method (Scheme A). In the following explanation, the salts of the compounds represented by formulas (II) and (III) may be the same ones as mentioned for the compounds represented by formula (I).

[Scheme A]



(The reference letters have the same definitions explained above.)

In this method, Compound (II) (meaning compounds represented by formula (II) and their salts) and Compound (III) (meaning compounds represented by formula (III) and their salts) are reacted to produce Compound (I).

The condensation reaction between Compound (II) and Compound (III) is conducted by ordinary peptide synthesis means. The peptide synthesis means may be carried out according to any desired publicly known method, for example, the method described by M. Bodansky and M.A. Ondetti, Peptide Synthesis, InterScience, New York, 1966; F.M. Finn and K. Hofmann, The Proteins, Vol.2, ed. by H. Nenrath and R.L. Hill, Academic Press Inc., New York, 1976; or N. Izumiya, "Peputido Gosei no Kiso to Jikken" [Peptide Synthesis Fundamentals and Experiments], Maruzen Publishing, 1985. There may be employed, for example, amide methods, chloride methods, acid anhydride methods, mixed acid anhydride methods, DCC methods, active ester methods, methods using Woodward K reagents, carbonyldiimidazole methods, oxidation-reduction methods, DCC/HONB methods or the like, as well as methods using diethylpyrocarbonate (DEPC). The condensation reaction may be

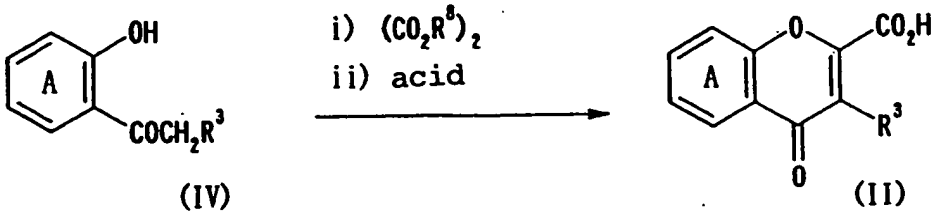
carried out in a solvent. As solvents there may be mentioned, for example, anhydrous or hydrous dimethylformamide, dimethylsulfoxide, pyridine, chloroform, dichloromethane, tetrahydrofuran, dioxane, acetonitrile and appropriate mixtures thereof. The reaction temperature will normally be from about -20°C to about 50°C, and preferably from -10°C to 30°C. The reaction time is about 1-100 hours, and preferably about 2-40 hours.

A different Compound (I) may also be produced from Compound (I) obtained in the above manner, also by a publicly known method (for example, oxidation reaction, reduction reaction, acylation reaction, esterification reaction, amidation reaction, etc.).

Compound (I) obtained in this manner may be isolated and purified by publicly known isolation and purification means, for example, by concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, solvent substitution, chromatography or the like.

The starting Compound (II) may be produced by a publicly known method, for example, the method described in the introduction to Progress in Medicinal Chemistry, Vol.9, p.65 (1973), in Liebigs Annalen der Chemie, p.1552 (1973) or in Journal of Chemical Society Parkin Transactions 1, p.2597 (1987). Specifically, it may be produced by the following Scheme B or Scheme C.

[Scheme B]



(IV) (II)

where R^8 represents a C_{1-10} alkyl group, and the other reference letters are as defined above.

As C_{1-10} alkyl groups represented by R^8 there may be mentioned the same ones as for R^1-R^3.

As compounds represented by formula (II) and their salts there may be mentioned, for example, 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid, 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid and 5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid, or their salts. 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid, 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid and 5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid, and their salts, are novel compounds.

In Scheme B, a compound represented by formula (IV) or its salt (hereunder also referred to as "Compound (IV)") is first reacted with an oxalic acid ester (first stage reaction), and then treated with an acid (second stage reaction) to produce Compound (II).

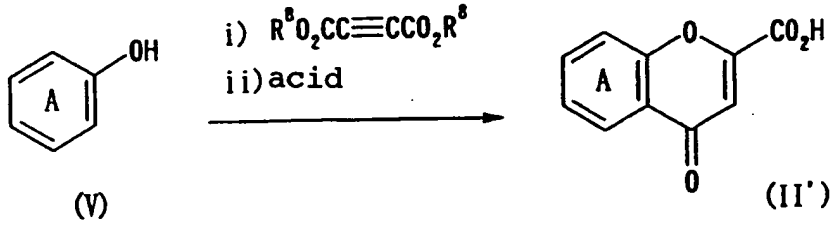
The first stage reaction is carried out in a solvent in the presence of a base. As solvents there may be mentioned aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, ethers such as diethyl ether, tetrahydrofuran and dioxane, alcohols such as methanol, ethanol, propanol and 2-methoxyethanol, N,N-dimethylformamide, dimethylsulfoxide, and mixtures thereof. As bases there may be mentioned sodium alkoxides such as sodium methoxide and sodium ethoxide, potassium alkoxides such as potassium ethoxide and potassium tert-butoxide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, and the like. The amount of oxalic acid ester used is about 1-3 molar equivalents with respect to Compound (IV), while the amount of the base used is about 1-10 molar equivalents and preferably about 2-5 molar equivalents, with respect to Compound (IV). The reaction is carried out at about -20°C to 150°C and preferably about 0°C to 120°C, for approximately 0.5-10 hours.

The compound obtained by the first stage reaction is then subjected to the second stage reaction to produce Compound

(II). The second stage reaction is carried out in an ether such as diethyl ether, tetrahydrofuran or dioxane, an alcohol such as methanol, ethanol, propanol or 2-methoxyethanol, acetic acid, N,N-dimethylformamide, dimethylsulfoxide, acetonitrile, 2-butanone, water or a mixture thereof, by heating with an inorganic acid such as hydrochloric acid or sulfuric acid. The amount of inorganic acid used is usually in a large excess, and the reaction is carried out at about 20°C to 180°C for approximately 0.5-30 hours.

The benzopyran derivative (II) or its salt obtained in this manner may be isolated and purified by publicly known isolation and purification means, for example, by concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, solvent substitution, chromatography or the like.

[Scheme C]



(V) (II')

where R^8 is as defined above.

In Scheme C, a compound represented by formula (V) or its salt (hereunder also referred to as "Compound (V)") is first reacted with an acetylenedicarboxylic acid ester (first stage reaction) and then treated with an acid (second stage reaction) to produce Compound (II') (meaning compounds represented by formula (II') and their salts).

The first stage reaction is carried out in a solvent in the presence of a base. As solvents there may be mentioned aromatic hydrocarbons such as benzene, toluene and xylene, halogenated hydrocarbons such as chloroform, dichloromethane, 1,2-dichloroethane and 1,1,2,2-tetrachloroethane, ethers such as diethyl ether, tetrahydrofuran and dioxane, alcohols such as methanol, ethanol, propanol and 2-methoxyethanol, N,N-

dimethylformamide, dimethylsulfoxide, and mixtures thereof. As bases there may be mentioned phase transfer catalysts such as tetrabutylammonium fluoride (TBAF), sodium alkoxides such as sodium methoxide and sodium ethoxide, potassium alkoxides such as potassium ethoxide and potassium tert-butoxide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide and the like. The amount of acetylenedicarboxylic acid ester used is about 1-3 molar equivalents with respect to Compound (V), while the amount of the base used is about 0.1-10 molar equivalents and preferably about 0.4-5 molar equivalents, with respect to Compound (V). The reaction is carried out at about -20°C to 150°C and preferably about 0°C to 120°C, for approximately 0.5-10 hours.

The compound obtained by the first stage reaction is then subjected to the second stage reaction to produce Compound (II'). The second stage reaction is carried out in an ether such as diethyl ether, tetrahydrofuran or dioxane, an alcohol such as methanol, ethanol, propanol or 2-methoxyethanol, acetic acid, N,N-dimethylformamide, dimethylsulfoxide, acetonitrile, 2-butanone, water or a mixture thereof, by heating with an inorganic acid such as hydrochloric acid or sulfuric acid. The amount of inorganic acid used is usually in a large excess, and the reaction is carried out at about 20°C to 120°C for approximately 0.5-30 hours.

The benzopyran derivative (II') or its salt obtained in this manner may be isolated and purified by publicly known isolation and purification means, for example, by concentration, concentration under reduced pressure, solvent extraction, crystallization, recrystallization, solvent substitution, chromatography or the like.

As prodrugs of the present invention Compound (I) there may be mentioned compounds which convert to Compound (I) by reaction with enzymes, gastric acid and the like under physiological conditions in the body, i.e., compounds which

convert to Compound (I) upon undergoing enzymatic oxidation, reduction, hydrolysis or the like, and compounds which convert to Compound (I) upon hydrolysis or the like by gastric acid, etc.

As Compound (I) prodrugs there may be mentioned compounds wherein the amino group of Compound (I) has been acylated, alkylated or phosphorylated (for example, compounds wherein the amino group of Compound (I) has been eicosanoylated, alanylated, pentylaminocarbonylated, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylated, tetrahydrofuranylated, pyrrolidylmethylated, pivaloyloxymethylated, tert-butylated, etc.); compounds wherein the hydroxyl group of Compound (I) has been acylated, alkylated, phosphorylated or borated (for example, compounds wherein the hydroxyl group of Compound (I) has been acetylated, palmitoylated, propanoylated, pivaloylated, succinylated, fumarylated, alanylated, dimethylaminomethylcarbonylated, etc.); compounds wherein the carboxyl group of Compound (I) has been esterified or amidated (for example, compounds wherein the carboxyl group of Compound (I) has been ethylesterified, phenylesterified, carboxymethylesterified, dimethylaminomethylesterified, pivaloyloxymethylesterified, ethoxycarbonyloxyethylesterified, phthalidylesterified, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methylesterified, cyclohexyloxycarbonylethylesterified methylamidated, etc.). These compounds may be produced from Compound (I) by publicly known methods.

The Compound (I) prodrugs may also be agents which convert to Compound (I) under physiological conditions as described in the 1990 Hirokawa Shoten publication "Iyakuhin no Kaihatsu" [Drug Development], Vol.7 "Bunshi Sekkei" [Molecular Design], pp.163-198.

Compound (I) may also be in the form of a hydrate.

Because Compound (I) of the invention exhibits excellent activity as an alkali phosphatase derivative, it has a powerful osteogenesis accelerating effect, osteoblast

differentiation inducing and accelerating effect, chondrogenesis accelerating effect and chondrocyte differentiation inducing and accelerating effect, and is a highly clinically useful substance in terms of safety, absorption (particularly oral absorption), bioavailability, etc. It is also nontoxic. Compound (I) of the invention can therefore be safely administered to mammals (for example, a human, rat, mouse, dog, rabbit, cat, cow, horse, pig, etc.).

Osteogenesis accelerators, bone disease prophylactic and treatment agents, bone fracture prophylactic and treatment agents and cartilage disease prophylactic and treatment agents containing Compound (I) of the invention having the aforementioned effects may be used as prophylactic and treatment agents for orthopedic bone and cartilage conditions such as fracture, refracture, bone loss, osteomalacia, Paget's bone disease, rigid spondylitis, rheumatoid arthritis, osteoarthritis, (for example, osteoarthrosis of the knee), cartilage-related osteoarthropathy and the like, and as bone tissue repair agents after surgery for multiple myeloma, lung cancer, breast cancer and the like. In the field of dentistry, they are expected to have applications for treatment of periodontal disease, repair of tissue loss by periodontal disease, stabilization of artificial dental roots, alveolar ridge formation, repair of cleft palate, and the like.

When Compound (I) of the invention is used as a prophylactic or treatment agent for osteoporosis, bone fracture, cartilage loss or the like, the dosage per person will differ depending on condition and body weight of the patient and the route of administration, but for oral administration it may be administered at about 1 to 500 mg, and preferably about 10 to 100 mg, in terms of the active component (Compound (I) of the invention) per person for adults (50 kg weight), divided in 1 to 3 doses.

For parenteral administration, it may be administered at about 1 to 300 mg, and preferably about 10 to 100 mg, in terms

of the active component (Compound (I) of the invention) per person for adults (50 kg weight), divided in 1 to 3 doses.

Compound (I) of the invention may also be used in combination with other bone resorption inhibitors or osteogenesis accelerators. As combination agents there may be mentioned, for example, D_3 vitamins (for example, 1á-hydroxyvitamin D_3, 1á,25-dihydroxyvitamin D_3, flocalcitriol, secalciferol, etc.), calcitonins (for example, eel calcitonin, salmon calcitonin, pig calcitonin, avicatonin, etc.), bisphosphonates (for example, etidronate, cimadronate, alendronate, tiludronate, risedronate, clodronate, etc.), sex hormone-related compounds (civolone, estradiol, osaterone, raloxifene, droloxifen, ormeloxifen, tamoxifen, mifepristone, etc.), ipriflavone, K_2 vitamins (for example, menatetrenone), sodium fluoride and parathyroid hormones (PTH) (for example, PTH (1-34), PTH (1-84), PTH (1-36), etc.).

Compound (I) of the invention may be formulated with a pharmaceutically acceptable carrier for oral or parenteral administration in the form of a solid preparation such as tablets, capsules, granules, powder, etc. or a liquid preparation such as a syrup, injection, or the like. It may also be prepared as a percutaneously administered formulation such as a patch, pap, ointment (including creams), plaster, tape, lotion, solution, suspension, emulsion, spray or the like.

As pharmaceutically acceptable carriers there may be used organic or inorganic carrier substances commonly employed as formulating materials, and these include excipients, gloss agents, binders and disintegrating agents for solid formulations, or solvents, dissolving aids, suspending agents, isotonizing agents, buffering agents and soothing agents for liquid formulations. If necessary, formulating additives such as preservatives, antioxidants, stabilizers, coloring agents, sweeteners and the like may also be used. As preferred examples of excipients there may be mentioned lactose,

saccharose, D-mannitol, starch, crystalline cellulose, light silicic anhydride and the like. As preferred examples of gloss agents there may be mentioned magnesium stearate, calcium stearate, talc, colloidal silica and the like. As preferred examples of binders there may be mentioned crystalline cellulose, á-converted starch, saccharose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone and the like. As preferred examples of disintegrating agents there may be mentioned starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, carboxymethyl starch sodium, low-substituted hydroxypropyl cellulose and the like. As preferred examples of solvents there may be mentioned injection water, alcohol, propylene glycol, macrogol, sesame oil, corn oil and the like.

As preferred examples of dissolving aids there may be mentioned polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate and the like. As preferred examples of suspending agents there may be mentioned surfactants such as stearyltriethanolamine, sodium lauryl sulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, benzethonium chloride and glyceryl monostearate, and hydrophilic polymeric substances such as polyvinyl alcohol, polyvinylpyrrolidone, carboxylmethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and the like. As preferred examples of isotonizing agents there may be mentioned sodium chloride, glycerin, D-mannitol and the like. As preferred examples of buffering agents there may be mentioned buffer solutions of phosphates, acetates, carbonates, citrates and the like. As preferred examples of soothing agents there may be mentioned benzyl alcohol and the like. As preferred examples of preservatives there may be mentioned paraoxybenzoic acid sters, chlorobutanol, benzyl alcohol,

phenethyl alcohol, dehydroacetic acid, sorbic acid and the like. As preferred examples of antioxidants there may be mentioned sulfurous acid salts, ascorbic acid and the like.

If necessary, an oral administration formulation may be prepared by coating by a publicly known method for flavor masking, enteric coating or sustained release. As coating agents there may be used for example, hydroxypropylmethyl cellulose, ethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, polyoxyethylene glycol, Tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, hydroxymethyl cellulose acetate succinate, Eudragit (methacrylic acid/acrylic acid copolymer by Rohm Inc. of Germany), and the like.

Compound (I) of the invention may be used not only as a formulation prepared by the aforementioned ordinary formulating techniques, but also as sustained release formulation prepared by sustained release techniques. As methods for preparing sustained release formulations there may be mentioned methods of dispersion in aliphatic polyesters such as lactic acid-glycolic acid copolymer by water drying, phase separation, spray drying, etc. as described in, for example, Japanese Unexamined Patent Publication HEI No. 9-263545. Sustained release formulations obtained by such methods may be locally administered in the form of microcapsules or suspensions of microspheres, for example.

Compound (I) of the invention is preferably added to a pharmaceutical composition together with polyethylene glycol as described in Japanese Unexamined Patent Publication HEI No. 10-338646.

For direct administration into a joint cavity as a local drug, it may be prepared by dispersion of Compound (I) using hyaluronic acid injection preparation (for example, Artz Injection by Kaken Pharmaceutical Co., Ltd.) as the dispersing medium. The hyaluronic acid used in the dispersing medium is preferably used in the form of a nontoxic salt, of which

examples include its alkali metal salts such as sodium and potassium salts and its alkaline earth metal salts such as magnesium and calcium salts, with the sodium salt being particularly preferred. The hyaluronic acid or its nontoxic salt may have a molecular weight of about 200,000 to 5 million (viscosity method), preferably about 500,000 to 3 million and more preferably about 700,000 to 2.5 million.

The final concentration of hyaluronic acid or sodium hyaluronate in the dispersing agent is preferably no more than 1% (w/v) in terms of appropriate viscosity and ease of handling and administration, and it is especially about 0.02-1% and more preferably about 0.1-1% (w/v).

A publicly known method may also be used to add a pH adjustor, local anesthetic, antibiotic, dissolving aid, isotonizing agent, adsorption inhibitor, glucosaminoglycan, polysaccharide or the like to the dispersing medium. As preferred examples there may be mentioned mannitol, sorbitol, table salt, glycine, ammonium acetate and water-soluble proteins that exhibit substantially no physiological activity and may be injected into the body. As glucosaminoglycans there may be mentioned hyaluronic acid, chondroitin, chondroitin sulfate A, chondroitin sulfate C, dermatan sulfate, heparin, heparin sulfate, keratan sulfate and the like. As polysaccharides there may be mentioned acidic polysaccharides such as alginic acid.

As water-soluble proteins there may be mentioned any ones that dissolve in water, physiological saline or buffer solution, such as human serum albumin, human serum globulin, collagen, gelatin and the like. The content of the water-soluble protein when added to the dispersing medium is preferably 0.05-50 mg, more preferably 0.5-20 mg and even more preferably 0.75-10 mg per single administration of the formulation.

As pH adjustors there may be mentioned glycine, ammonium acetate, citric acid, hydrochloric acid and sodium hydroxide,

for example. As local anesthetics there may be mentioned chlorobutanol and xylocaine hydrochloride, for example. As antibiotics there may be mentioned gentamycin, for example. As dissolving aids there may be mentioned, in addition to the above, also glycerin and polyethylene glycol 400, for example. As isotonizing agents there may be mentioned, in addition to the above, also sorbitol, for example. As adsorption inhibitors there may be mentioned polyoxyethylene sorbitan monooleate, for example.

The formulation may also contain phosphoric acid or its salts (for example, sodium phosphate, potassium phosphate, etc.). When phosphoric acid or its salts are included in an injection, the sodium phosphate or potassium phosphate concentration of the injection is usually from about 0.1 mM to 500 mM, and preferably from about 1 mM to 100 mM.

Examples

The present invention will now be explained in greater detail by the following reference examples, examples and experiment examples, with the understanding that the invention is in no way limited thereby.

Reference Examples

Production of N-methoxy-N-methyl-2-methoxymethoxy-5,6-methylenedioxybenzamide:

A mixed solution of N,N-dimethylformamide (DMF) (100 ml) containing 2-methoxymethoxy-5,6-methylenedioxybenzoic acid (9.05 g), N,O-dimethylhydroxylamine hydrochloride (5.13 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (8.53 g), triethylamine (7.5 ml) and 1-hydroxybenzotriazole (HOBt) (5.95 g) was stirred at room temperature for 12 hours and then diluted with a mixed solution of ethyl acetate (100 ml) and water (100 ml), and after washing the organic layer with a saturated sodium bicarbonate aqueous solution, water, 1 N hydrochloric acid, water and saturated saline in that order,

it was dried ($MgSO_4$) and the solvent was distilled off. The residue was purified by silica gel chromatography to obtain the title compound as a colorless oil (4.95 g, 46% yield). ^1H NMR ($CDCl_3$)ä: 3.39 (3H,s), 3.47 (3H,s), 3.58 (3H,s), 5.11 (2H,s), 5.98 (2H,s), 6.60 (1H,d,J=8.6 Hz), 6.74 (1H,d,J=8.6 Hz).

Production of 2'-methoxymethoxy-5',6'-methylenedioxy-acetophenone:

An ether solution (100 ml) containing N-methoxy-N-methyl-2-methoxymethoxy-5,6-methylenedioxybenzamide (4.95 g) was cooled to -30°C and methylmagnesium bromide (3.0 M ether solution, 6.25 ml) was added prior to stirring for one hour. After again adding methylmagnesium bromide (3.0 M ether solution, 3 ml) and stirring for one hour, an oxalic acid aqueous solution was added and extraction was performed with ethyl acetate. The extract was washed with a saturated sodium bicarbonate aqueous solution, water, 1 N hydrochloric acid solution, water and saturated saline in that order and dried ($MgSO_4$), and then the solvent was distilled off. The residue was purified by silica gel chromatography to obtain the title compound as a colorless oil (2.1 g, 51% yield). ^1H NMR ($CDCl_3$)ä: 3.39 (3H,s), 3.47 (3H,s), 3.58 (3H,s), 5.11 (2H,s), 5.98 (2H,s), 6.60 (1H,d,J=8.6 Hz), 6.74 (1H,d,J=8.6 Hz).

Production of 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

To a solution of sodium (0.65 g) dissolved in ethanol (30 ml) there were added 2'-methoxymethoxy-5',6'-methylenedioxyacetophenone (1.4 g) and diethyl oxalate (1.64 g), and then the mixture was heated to reflux for 2 hours. After cooling the reaction solution, the precipitated salt was filtered out, dissolved in 2 N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and saturated saline and dried ($MgSO_4$), and then the solvent was

distilled off. The obtained oil was dissolved in acetic acid (6 ml) and hydrochloric acid (6 ml), heated to reflux for 2 hours and cooled, after which the precipitated crystals were filt red off to obtain the title compound (1.36 g, 72% yield). ^{1}H NMR ($CDCl_3$)ä: 6.26 (2H,s), 6.73 (1H,s), 7.16 (1H,d,J=8.8 Hz), 7.41 (1H,d,J=8.8 Hz).

Production of 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

Aluminum chloride (0.48 g) was added to a mixed solution comprising a dichloroethane solution (20 ml) containing 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.475 g), and the mixture was stirred at room temperature for 2 hours. The reaction solution was poured into 2 N hydrochloric acid and extracted with chloroform. The extract was washed with water and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain the title compound (0.169 g, 38% yield). ^{1}H NMR (DMSO-d_6)ä: 6.85 (1H,s), 7.06 (1H,d,J=9.2 Hz), 7.33 (1H,d,J=9.2 Hz), 9.58 (1H,s), 12.09 (1H,s).

Production of 5-methoxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid:

To a solution of sodium (0.41 g) dissolved in ethanol (30 ml) there were added 2'-hydroxy-6'-methoxy-4'-methylacetophenone (1.08 g) and diethyl oxalate (0.96 g), and then the mixture was heated to reflux for 2 hours. After cooling the reaction solution, the precipitated salt was filtered out, dissolved in 2 N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained oil was dissolved in acetic acid (3 ml) and hydrochloric acid (3 ml), heated to reflux for 2 hours and cooled, after which the precipitated crystals were filtered off to obtain the title compound (0.78 g, 55% yield).

^{1}H NMR (DMSO-d_6)ä: 2.69 (3H,s), 3.89 (3H,s), 6.72 (1H,s), 6.86 (1H,d,J=2.2 Hz), 7.01 (1H,d,J=2.2 Hz).

Production of 5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid:

Aluminum chloride (0.63 g) was added to a mixed solution comprising a dichloroethane solution (20 ml) containing 5-methoxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.555 g), and the mixture was stirred at room temperature for 2 hours. The reaction solution was poured into 2 N hydrochloric acid and extracted with chloroform. The extract was washed with water and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain the title compound (0.405 g, 78% yield). ^{1}H NMR (DMSO-d_6)ä: 2.66 (3H,s), 6.68 (1H,s), 6.69 (1H,d,J=2.2 Hz), 6.738 (1H,d,J=2.2 Hz).

Production of 5-butyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

a) 5-butyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester:

Butyryl chloride (1.1 ml) was added to a pyridine solution (10 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester (1.00 g) and 4-(N,N-dimethylamino)pyridine (0.042 g) at room temperature, and after stirring for 14 hours, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and an ammonium chloride aqueous solution in that order and dried ($MgSO_4$), and then the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography and 1.10 g of the target compound was obtained as colorless crystals from the fraction obtained with ethyl acetate/n-hexane (1:4) (89% yi ld). mp 103-105°C

b) 5-butyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

An ethyl acetate solution (100 ml) containing 5-butyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester (1.00 g) and palladium carbon (5%, 0.20 g) was stirred for 30 minutes under a hydrogen atmosphere. The insoluble portion was filtered out and the filtrate was concentrated under reduced pressure to obtain 0.72 g of the title compound as colorless crystals (95% yield). mp 218-220°C

Production of 5-isobutyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

a) 5-isobutyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester:

Isobutyryl chloride (1.1 ml) was added to a pyridine solution (10 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester (1.00 g) and 4-(N,N-dimethylamino)pyridine (0.042 g) at room temperature, and after stirring for 14 hours, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and an ammonium chloride aqueous solution in that order and dried ($MgSO_4$), and then the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography and 1.20 g of the target compound was obtained as colorless crystals from the fraction obtained with ethyl acetate/n-hexane (1:4) (97% yield). mp 90-92°C

b) 5-isobutyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

An ethyl acetate solution (100 ml) containing 5-isobutyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester (1.00 g) and palladium carbon (5%, 0.20 g) was stirred for 30 minutes under a hydrogen atmosphere. The insoluble portion was filtered out and the filtrate was concentrated under reduced pressure to obtain 0.64 g of the title compound

as colorless crystals (85% yield). mp 206-208°C

Production of 5-diethylcarbamoyloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

a) 5-diethylcarbamoyloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester:

Diethylcarbamoyl chloride (0.86 ml) was added on ice to a THF solution (30 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester (1.00 g), 4-(N,N-dimethylamino)pyridine (0.082 g) and triethylamine (0.94 ml), and after stirring for 24 hours at 45°C, the reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and an ammonium chloride aqueous solution in that order and dried ($MgSO_4$), and then the solvent was distilled off under reduced pressure to obtain 1.25 g of the title compound as colorless crystals (94% yield). mp 104-106°C

b) 5-diethylcarbamoyloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid:

An ethyl acetate solution (100 ml) containing 5-diethylcarbamoyloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid benzyl ester (1.13 g) and palladium carbon (5%, 0.20 g) was stirred for 30 minutes under a hydrogen atmosphere. The insoluble portion was filtered out and the filtrate was concentrated under reduced pressure to obtain 0.82 g of the title compound as colorless crystals (94% yield). mp 189-191°C

Example 1

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.162 g) was added to a DMF solution (10 ml) containing 4-oxo-4H-1-benzopyran-2-

carboxylic acid (0.191 g), 5-(4-aminobenzyl)-2,4-dioxothiazolidine (0.223 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.288 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with chloroform. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The residue was purified by silica gel column chromatography and the obtained crystals were washed with ethyl acetate to obtain 0.117 g of the title compound (30% yield). mp 284-287°C

Example 2

Production of N-[4-[(2,4-dioxo-1,3-oxazolidin-5-yl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.290 g) was added to a DMF solution (20 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.270 g), 5-(4-aminobenzyl)-2,4-dioxooxazolidine (0.295 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.550 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into an ethyl acetate-water mixture. The ethyl acetate layer was washed with a diluted hydrochloric acid aqueous solution, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with isopropyl ether to obtain 0.372 g of the title compound (70% yield). mp 265-267°C

Example 3

Production of 4-oxo-N-[4-[(2-oxo-1,3-oxazolidin-3-yl)methyl] ph nyl]-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazol (HOBt) (0.288 g) was added to a DMF solution (6 ml) containing 4-oxo-4H-1-benzopyran-2-

carboxylic acid (0.371 g), 3-(4-aminobenzyl)-2-oxazolidone (0.375 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.411 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with water, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethyl acetate to obtain 0.591 g of the title compound (83% yield). mp 237-238°C

Example 4

Production of N-[4-[(2,6-dioxo-1-piperidinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.245 g) was added to a DMF solution (20 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.23 g), 1-(4-aminobenzyl)glutarimide hydrochloride (0.300 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.464 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with isopropyl ether to obtain 0.4 g of the title compound (87% yield). mp 190-192°C

Example 5

Production of N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.426 g) was added to a DMF solution (15 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.4 g), 4-(4-aminobenzyl)morpholine (0.385 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (0.805 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into a mixed solution of water and ethyl acetate and extracted with ethyl acetate. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with isopropyl ether-hexane to obtain 0.65 g of the title compound (89% yield). mp 201-203°C

Example 6

Production of 4-oxo-N-[4-[(4-thiomorpholinyl)methyl]phenyl]-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.262 g) was added to a DMF solution (10 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.296 g), 1-(4-aminobenzyl)thiomorpholine (0.361 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.366 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with ethyl acetate to obtain 0.447 g of the title compound (76% yield). mp 212-213°C

Example 7

Production of 4-oxo-N-[4-[(4-oxo-1-piperidinyl)methyl]phenyl]-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.262 g) was added to a DMF solution (6 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.298 g), 1-(4-aminobenzyl)-4-oxopiperidine (0.348 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.372 g), the mixture was stirred at room

temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate to obtain 0.113 g of the title compound (19% yield). mp 183-185°C

Example 8

Production of 4-oxo-N-[4-[(1,3-thiazolidin-3-yl)methyl] phenyl]-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.2 g) was added to a DMF solution (6 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.28 g), 1-(4-aminobenzyl)-1,3-thiazolidine (0.25 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.293 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate to obtain 0.347 g of the title compound (64% yield). mp 203-204°C

Example 9

Production of N-[4-[(1-piperazinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

A 4 N hydrochloric acid-ethyl acetate solution (3 ml) was added dropwise to a dichloromethane solution containing 4-[4-[(4-oxo-4H-1-benzopyran-2-carbonyl)amino]benzyl] piperidine-1-carboxylic acid tert-butyl ester (0.2 g), and the mixture was stirred at room temperature for 3 days. After concentrating the reaction solution, the residue was dissolved in a 2 N

sodium hydroxide aqueous solution and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The precipitated crystals were filtered off and washed with isopropyl ether to obtain 0.09 g of the title compound (59% yield). mp 138-140°C

Example 10

Production of 4-[4-[(4-oxo-4H-1-benzopyran-2-carbonyl)amino] benzyl]piperazine-1-carboxylic acid tert-butyl ester:

Oxalyl chloride (0.32 ml) was added on ice to a THF solution (30 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.46 g) and 3 drops of DMF, and the mixture was stirred at 0°C for one hour. The reaction solution was concentrated under reduced pressure, the residue was dissolved in THF (20 ml), and then 4-(4-aminobenzyl)piperazine-1-carboxylic acid tert-butyl ester (0.7 g) and triethylamine (0.84 ml) were added in that order and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with ethyl acetate. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The residue was recrystallized from isopropyl ether to obtain 0.64 g of the title compound (58% yield). mp 197-199°C

Example 11

Production of N-[4-[(2,5-dioxo-1-imidazolidinyl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.426 g) was added to a DMF solution (15 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.4 g), 4-(2,5-dioxo-1-imidazolidinyl)methylaniline (0.561 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.805 g), the

mixture was stirred at room temperature for 14 hours, and then the reaction solution was poured into a mixed solution of water and ethyl acetate and the crystals were filtered off. The obtained crystals were recrystallized from DMF-ethanol to obtain 0.530 g of the title compound (67% yield). mp 258-261°C

Example 12

Production of N-[4-[(3-methyl-2,5-dioxo-1-imidazolidinyl) methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.2 g) was added to a DMF solution (10 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.28 g), 3-(4-aminobenzyl)-1-methylhydantoin (0.323 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.294 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethyl acetate to obtain 0.369 g of the title compound (64% yield). mp 195-196°C

Example 13

Production of N-[4-[(2,4-dioxo-1,3-oxazolidin-3-yl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.202 g) was added to a DMF solution (10 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.28 g), 1-(4-aminobenzyl)-2,4-dioxazolidine (0.304 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.293 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous

solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate to obtain 0.451 g of the title compound (64% yield). mp 261-262°C

Example 14

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-3-yl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.426 g) was added to a DMF solution (20 ml) containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.4 g), 3-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.47 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.805 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into a mixed solution of water and ethyl acetate and extracted with ethyl acetate. The extract was washed with a 1 N hydrochloric acid aqueous solution, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with isopropyl ether-hexane to obtain 0.725 g of the title compound (88% yield). mp 206-208°C

Example 15

Production of N-[4-[(3-methyl-2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

A separately prepared diazomethane-ether solution was added in excess to a THF suspension (30 ml) containing N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide (0.394 g) at 0°C, and then the mixture was stirred at room temperature for 3 hours. After concentrating the reaction solution and diluting it with a mixed solution of THF-ethyl acetate, it was washed with an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.36 g of the title compound (88% yield). mp 214-216°C

Example 16

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.492 g) was added to a DMF solution (20 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.23 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.647 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.932 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-acetone to obtain 0.636 g of the title compound (64% yield). mp 284-286°C

Example 17

Production of 5,6-dihydroxy-N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.22 g) was added to a DMF solution (8 ml) containing 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.325 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.321 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.311 g), the mixture was stirred at room temperature for 16 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate to obtain 0.178 g of the title compound (29% yield). mp 280°C (decomposition)

Example 18

Production of 5,7-dihydroxy-N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.053 g) was added to a DMF solution (8 ml) containing 5,7-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.069 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.069 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.066 g), the mixture was stirred at room temperature for 15 hours and then the reaction solution was poured into water and the precipitated crystals were filtered off. The obtained crystals were recrystallized from THF-methanol to obtain 0.11 g of the title compound (83% yield). mp > 300°C

Example 19

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-5-hydroxy-7-methoxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.107 g) was added to a DMF solution (15 ml) containing 5-hydroxy-7-methoxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.15 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.141 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.134 g), the mixture was stirred at room temperature for 15 hours and then the reaction solution was poured into water and extracted with ethyl acetate. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethyl acetate to obtain 0.22 g of the title compound (79% yield). mp 255-256°C

Example 20

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-

carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.139 g) was added to a DMF solution (6 ml) containing 5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.204 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.206 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.198 g), the mixture was stirred at room temperature for 14 hours and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF to obtain 0.269 g of the title compound (68% yield). mp 290°C (decomposition)

Example 21

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-5-methoxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.13 g) was added to a DMF solution (6 ml) containing 5-methoxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.205 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.195 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.186 g), and the mixture was stirred at room temperature for 16 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF to obtain 0.269 g of the title compound (70% yield). mp 267-269°C

Example 22

Production of 6,7-dihydroxy-N-[4-[(2,4-dioxo-1,3-thiazolidin-

5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.115 g) was added to a DMF solution (15 ml) containing 6,7-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.15 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.15 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.145 g), and the mixture was stirred at room temperature for 15 hours. The reaction solution was diluted with a mixed solution of ethyl acetate and THF, washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate/n-hexane to obtain 0.097 g of the title compound (34% yield). mp > 300°C

Example 23

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-5,7-dimethoxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.067 g) was added to a DMF solution (10 ml) containing 5,7-dimethoxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.099 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.088 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.084 g), and the mixture was stirred at room temperature for 15 hours. The reaction solution was diluted with a mixed solution of ethyl acetate and THF, washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from DMF-water to obtain 0.129 g of the title compound (72% yield). mp > 300°C

Example 24

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-5-methoxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.078 g) was added to a DMF solution (10 ml) containing 5-methoxy-4-oxo-4H-1-

benzopyran-2-carboxylic acid (0.101 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.11 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.097 g), and the mixture was stirred at room temperature for 15 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethyl acetate to obtain 0.108 g of the title compound (56% yield). mp 293-294°C

Example 25

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-5-hydroxy-4-oxo-10-propyl-6,7,8,9-tetrahydro-4H-naphtho[2,3-b]pyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.112 g) was added to a DMF solution (12 ml) containing 5-hydroxy-4-oxo-10-propyl-6,7,8,9-tetrahydro-4H-naphtho[2,3-b]pyran-2-carboxylic acid (0.2 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.154 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.14 g), and the mixture was stirred at room temperature for 15 hours. The reaction solution was diluted with a mixed solution of ethyl acetate and THF, washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate/n-hexane to obtain 0.281 g of the title compound (84% yield). mp 224-225°C

Example 26

Production of 6,8-dibromo-N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a

DMF solution (15 ml) containing 6,8-dibromo-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.364 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.23 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained residue was purified by silica gel column chromatography to obtain 0.07 g of the title compound (11% yield). mp 283-285°C

Example 27

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.19 g) was added to a DMF solution (10 ml) containing 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.33 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.306 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.31 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF to obtain 0.309 g of the title compound (50% yield). mp > 300°C

Example 28

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-6-methyl-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a

DMF solution (10 ml) containing 6-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.205 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.23 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethanol to obtain 0.28 g of the title compound (69% yield). mp 260°C (decomposition)

Example 29

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-8-methyl-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a DMF solution (10 ml) containing 8-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.207 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.222 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.193 g of the title compound (47% yield). mp 305-307°C

Example 30

Production of 6-bromo-N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a DMF solution (10 ml) containing 6-bromo-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.269 g), 5-(4-aminobenzyl)-2,4-

dioxothiazolidine (0.23 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), the mixture was stirred at room temperature for 14 hours, and then the reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethanol to obtain 0.266 g of the title compound (56% yield). mp 281-283°C

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Example 31

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-6-fluoro-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.154 g) was added to a DMF solution (4 ml) containing 6-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.214 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.226 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.224 g), and the mixture was stirred at room temperature for 60 hours. The reaction solution was poured into water and the precipitated crystals were washed with water, ethanol and isopropyl ether to obtain 0.39 g of the title compound (93% yield). mp 285-287°C

Example 32

Production of 8-bromo-N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

Oxalyl chloride (0.14 ml) was added on ice to a THF solution containing 8-bromo-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.269 g) and DMF (3 drops), and the mixture was stirred at 0°C for one hour. The reaction solution was concentrated under reduced pressure, the residue was dissolved in THF (10 ml), and then 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.333 g) and triethylamine (0.42 ml) were added in that order and the mixture was stirred at room temperature for 14 hours.

The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.216 g of the title compound (46% yield). mp 293-295°C

Example 33

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-7-fluoro-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.149 g) was added to a DMF solution (5 ml) containing 7-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.207 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.223 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.321 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate to obtain 0.369 g of the title compound (90% yield). mp 247-249°C

Example 34

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-5-fluoro-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.155 g) was added to a DMF solution (5 ml) containing 5-fluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.213 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.228 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.218 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed

with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with a mixed solvent of ethanol-isopropyl ether to obtain 0.418 g of the title compound (99% yield). mp 282-283°C

Example 35

Production of 5,7-difluoro-N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.161 g) was added to a DMF solution (5 ml) containing 5,7-difluoro-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.246 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.244 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.2313 g), and the mixture was stirred at room temperature for 16 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF to obtain 0.44 g of the title compound (89% yield). mp 280-282°C

Example 36

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-8-phenyl-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.2 g) was added to a DMF solution (10 ml) containing 8-phenyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.27 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.23 g) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.38 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl ac tate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous

solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.28 g of the title compound as an amorphous powder (60% yield).

Example 37

Production of N-[4-[(2,4-dioxo-1,3-thiazolidin-5-yl)methyl] phenyl]-7-phenyl-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.149 g) was added to a DMF solution (10 ml) containing 7-phenyl-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.268 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.223 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.218 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with diluted hydrochloric acid, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-ethanol to obtain 0.39 g of the title compound (82% yield). mp 235-237°C

Example 38

Production of N-[4-[(2,4-dioxo-1,3-oxazolidin-5-yl)methyl] phenyl]-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a DMF solution (15 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.206 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-oxazolidine (0.21 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained residue was purified by silica

gel column chromatography to obtain 0.216 g of the title compound (55% yield). mp 298-300°C

Example 39

Production of 5-hydroxy-N-[4-(4-morpholinylmethyl)phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.296 g) was added to a DMF solution (20 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.3 g), 4-(4-aminobenzyl)morpholine (0.308 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.56 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium hydroxide aqueous solution and saturated saline and dried ($MgSO_4$), and then the oil obtained by distilling off the solvent was crystallized from isopropyl ether to obtain 0.4 g of the title compound (72% yield). mp 200-202°C

Example 40

Production of 5,6-dihydroxy-N-[4-[(4-morpholinyl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.12 g) was added to a DMF solution (6 ml) containing 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.169 g), 4-(4-aminobenzyl)morpholine (0.146 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.16 g), and the mixture was stirred at room temperature for 16 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from ethyl acetate to obtain 0.05

g of the title compound (16% yield). mp 235-237°C

Example 41

Production of 5,7-dihydroxy-N-[4-[(4-morpholinyl)methyl] phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.154 g) was added to a DMF solution (6 ml) containing 5,7-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.225 g), 4-(4-aminobenzyl)morpholine (0.198 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.227 g), and the mixture was stirred at room temperature for 14 hours. After pouring the reaction solution into water and filtering off the precipitated crystals, they were washed with ethanol and water to obtain 0.240 g of the title compound (60% yield). mp 207-209°C

Example 42

Production of N-methyl-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide hydrochloride:

Oxalyl chloride (0.13 ml) was added on ice to a THF solution containing 4-oxo-4H-1-benzopyran-2-carboxylic acid (0.19 g) and DMF (3 drops), and the mixture was stirred at 0°C for one hour. The reaction solution was concentrated under reduced pressure, the residue was dissolved in THF (10 ml), and then 4-(4-methylaminobenzyl)morpholine (0.203 g) and triethylamine (0.28 ml) were added in that order and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The residue was purified by silica gel column chromatography. The obtained oil (0.4 g) was dissolved in ethyl acetate (2 ml), and then a 4 N hydrochloric acid/ethyl acetate solution (0.5 ml) was added dropwise thereto and the

pr cipitated crystals were filtered off to obtain 0.315 g of the title compound (76% yield). mp 230°C (decomposition)

Example 43

Production of 5-hydroxy-N-methyl-N-[4-(4-morpholinylmethyl) phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide hydrochloride:

Oxalyl chloride (0.22 ml) was added on ice to a THF solution containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.206 g) and DMF (3 drops), and the mixture was stirred at 0°C for one hour. The reaction solution was concentrated under reduced pressure, the residue was dissolved in THF (10 ml), and then 4-(4-methylaminobenzyl)morpholine (0.203 g) and triethylamine (0.28 ml) were added in that order and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The residue was purified by silica gel column chromatography. The obtained oil (0.15 g) was dissolved in ethyl acetate (2 ml), and then a 4 N hydrochloric acid/ethyl acetate solution (0.5 ml) was added dropwise thereto and the precipitated crystals were filtered off to obtain 0.154 g of the title compound (36% yield). mp 216°C (decomposition)

Example 44

Production of 5-hydroxy-4-oxo-N-[4-(1-piperidinylmethyl) phenyl]-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a DMF solution (15 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.206 g), 1-(4-aminobenzyl)piperidine (0.19 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), and th mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a

mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with isopropyl ether to obtain 0.261 g of the title compound (69% yield). mp 175-176°C

Example 45

Production of 5-hydroxy-4-oxo-N-[4-[[4-(methylsulfonyl)-1-piperazinyl]methyl]phenyl]-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.203 g) was added to a DMF solution (15 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.206 g), 4-[[4-(methylsulfonyl)-1-piperazinyl]methyl]aniline (0.19 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate and THF. The extract was washed with a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were washed with isopropyl ether to obtain 0.261 g of the title compound (69% yield). mp 175-176°C

Example 46

Production of N-[4-[[(4-formyl)-1-piperazinyl]methyl]phenyl]-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide:

1-Hydroxybenzotriazole (HOBt) (0.112 g) was added to a DMF solution (5 ml) containing 5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.113 g), 4-(4-aminobenzyl)-1-piperazinecarbaldehyde (0.223 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.125 g), and the mixture was stirred at room temperature for 2 days. The reaction solution was poured into wat r and extracted with a mixed solution of THF-ethyl acetate. The extract was washed

with a sodium bicarbonate aqueous solution, an ammonium chloride aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.053 g of the title compound (23% yield). mp 240°C (decomposition)

Example 47

Production of N-(4-(2,4-dioxothiazolidin-5-ylmethyl)phenyl)-5-acetoxy-4-oxo-4H-1-benzopyran-2-carboxamide:

Trimethylsilyl trifluoromethanesulfonate (TMSOTf)(0.43 ml) was added to an ethyl acetate solution (30 ml) containing N-(4-(2,4-dioxothiazolidin-5-ylmethyl)phenyl)-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide (0.329 g) and acetic anhydride (0.23 ml), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with water, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.35 g of the title compound (95% yield). mp 257-260°C

Example 48

Production of N-(4-(2,4-dioxothiazolidin-5-ylmethyl)phenyl)-5-butyryloxy-4-oxo-4H-1-benzopyran-2-carboxamide:

Oxalyl chloride (0.14 ml) was added on ice to a THF solution (10 ml) containing 5-butyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.28 g) and DMF (3 drops), and the mixture was stirred for one hour. After the reaction solution was first concentrated to dryness, THF (10 ml) was added, a THF solution (5 ml) containing 5-(4-aminobenzyl)-2,4-dioxothiazolidine (0.24 g) and triethylamine (0.42 ml) was added thereto, and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with diluted hydrochloric acid, water, a sodium bicarbonate aqueous solution and saturated saline and

dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-isopropyl ether to obtain 0.32 g of the title compound (67% yield). mp 249-250°C

Example 49

Production of N-(4-(2,4-dioxothiazolidin-5-ylmethyl)phenyl)-5-isobutyryloxy-4-oxo-4H-1-benzopyran-2-carboxamide:

Oxalyl chloride (0.14 ml) was added on ice to a THF solution (10 ml) containing 5-isobutyryloxy-4-oxo-4H-1-benzopyran-2-carboxylic acid (0.28 g) and DMF (3 drops), and the mixture was stirred for one hour. After the reaction solution was first concentrated to dryness, THF (10 ml) was added, a THF solution (5 ml) containing 5-(4-aminobenzyl)-2,4-dioxothiazolidine (0.24 g) and triethylamine (0.42 ml) was added thereto, and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed with diluted hydrochloric acid, water, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off. The obtained crystals were recrystallized from THF-isopropyl ether to obtain 0.18 g of the title compound (38% yield). mp 273-275°C

Example 50

Production of 2-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenyl] carbamoyl]-4-oxo-4H-1-benzopyran-5-yl diethylcarbamate ester:

1-Hydroxybenzotriazole (0.10 g) was added to a DMF solution (10 ml) containing carboxylic acid (0.15 g), 5-(4-aminobenzyl)-2,4-dioxothiazolidine (0.22 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.29 g), and the mixture was stirred at room temperature for 14 hours. The reaction solution was poured into water and extracted with a mixed solution of ethyl acetate-THF. The extract was washed

with diluted hydrochloric acid, water, a sodium bicarbonate aqueous solution and saturated saline and dried ($MgSO_4$), and then the solvent was distilled off to obtain 0.15 g of the title compound (57% yield). mp 228-230°C

Production Example 1

After combining 10 mg of the compound obtained in Example 1, 90 mg of lactose, 70 mg of fine crystalline cellulose and 5 mg of magnesium stearate, the mixture was granulated. After then adding 5 mg of magnesium stearate thereto, the entire amount was encapsulated into a gelatin capsule.

Production Example 2

After combining 10 mg of the compound obtained in Example 16, 35 mg of lactose, 150 mg of corn starch, 20 mg of fine crystalline cellulose and 2.5 mg of magnesium stearate, the mixture was granulated. After then mixing 10 mg of fine crystalline cellulose and 2.5 mg of magnesium stearate with the granules, they were compression molded into a tablet.

Production Example 3

After dissolving 10 mg of the compound obtained in Example 16, 100 mg of inosit and 20 mg of benzyl alcohol in distilled water for injection to a total amount of 2 ml, the mixture was filled into an ampule. The entire procedure was carried out under sterile conditions.

Production Example 4

After combining 10 mg of the compound obtained in Example 16, 35 mg of lactose, 150 mg of corn starch, 20 mg of fine crystalline cellulose and 2.5 mg of magnesium stearate, the mixture was granulated. After then mixing 10 mg of fine crystalline cellulose and 2.5 mg of magnesium stearate with the granules, they were compression molded into a tablet.

Test Example 1

Osteogenesis accelerating effect:

Interstitial cells prepared from the femoral bone marrow of healthy rats were used for measurement of alkali phosphatase activity as an index of bone formation. Specifically, following the method of Maniatopoulos et al. (Cell Tissue Research, Vol.254, p.317 (1988)), interstitial cells were prepared from the femoral bone marrow of 7-week-old male Sprague-Dawley rats, and were cultured in á-MEM (minimum essential medium) containing dexamethasone (10^{-7} M) and â-glycerophosphoric acid (10^{-2} M) in order to form calcified osteoid tissue. After one week, the confluent primary cells were treated with a 0.25% trypsin/0.2% EDTA solution and collected, and then subcultured in a culturing dish at a cell density of 1.6×10^{-4} cells/cm^2 (at day 0 of culturing). The test compound (10^{-5} M) was added to the culture solution from the second day of culturing, and the culturing was continued for an additional 5 days. After washing the cells with phosphate buffer solution, 0.2% Nonidet P-40 was added, the cells were homogenized and centrifuged at 3000 rpm for 10 minutes, and the resulting supernatant was used for measurement of the alkali phosphatase activity according to the method of Lowry et al. (Journal of Biological Chemistry, Vol.207, p.19 (1954)). The measured values are expressed in Tables 1 and 2 as the mean ±SE. The statistical analysis was according to the Student's t-test.

Table 1

Compound	Concentration (M)	Alkali phosphatase activity (A_{405})
Example No. 1	10^{-5}	0.564 ± 0.041**
Example No. 2	10^{-5}	0.310 ± 0.008**
Example No. 5	10^{-5}	0.558 ± 0.040**
Control	not added	0.175 ± 0.009

Mean ±S.E. (n=4), **: $p<0.01$ vs control (Student's t-test)

Table 2

Compound	Concentration (M)	Alkali phosphatase activity (A_{405})
Example No. 16	10^{-5}	0.720 ± 0.033**
Example No. 18	10^{-5}	0.720 ± 0.037**
Control	not added	0.180 ± 0.008

Mean ±S.E. (n=4), **: $p<0.01$ vs control (Student's t-test)

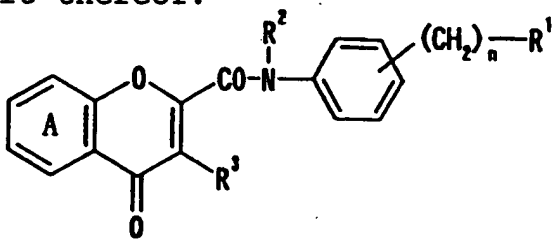
The results in Tables 1 and 2 demonstrate that the compounds of the invention exhibit an excellent osteogenesis accelerating effect.

Industrial Applicability

Compound (I) of the present invention has a powerful osteogenesis accelerating effect, chondrogenesis accelerating effect, chondroclastic inhibiting effect and chondrocyte differentiation inducing and accelerating effect, while also exhibiting excellent clinically useful properties such as stability, absorption (especially oral absorption) and bioavailability. It is therefore useful as a prophylactic and treatment agent for bone and cartilage conditions such as osteoporosis, fracture, cartilage deficiency, cartilage-related rheumatoid arthritis and cartilage-related osteoarthritis.

CLAIMS

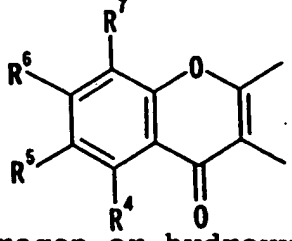
1. A chromone derivative represented by the following formula, or a salt thereof:



where ring A represents an optionally substituted benzene ring, R^1 represents an optionally substituted nonaromatic heterocyclic group, R^2 represents a hydrogen atom or hydrocarbon group, R^3 represents a hydrogen atom, hydrocarbon group or halogen, and n is an integer of 0 to 3.

2. A compound according to claim 1 or a salt thereof, wherein ring A is a benzene ring optionally substituted with 1 to 3 substituents selected from among hydroxy, acyloxy, mercapto, halogens, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} alkylthio and alkylenedioxy represented by the formula $-O-(CH_2)_m-O-$ (where m is an integer of 1 to 4), R^2 is hydrogen or C_{1-6} alkyl and R^3 is hydrogen.

3. A compound according to claim 1 or a salt thereof, wherein the partial structure including ring A is represented by the formula:



where R^4 represents hydrogen or hydroxyl, and R^5-R^7 each represent hydrogen, a halogen, C_{1-10} alkyl or C_{1-10} alkoxy and are either the same or different,
R^2 is hydrogen or a C_{1-6} alkyl and R^3 is hydrogen.

4. A compound according to claim 1 or a salt thereof, wherein the nonaromatic heterocyclic group for the optionally substituted nonaromatic group represented by R^1 is a 5- to 7-membered nonaromatic heterocyclic group containing from 1 to 4 hetero atoms selected from among nitrogen, sulfur and oxygen.

5. A compound according to claim 4 or a salt thereof, wherein the 5- to 7-membered nonaromatic heterocyclic group for the optionally substituted 5- to 7-membered nonaromatic heterocyclic group is a 5- to 7-membered nonaromatic heterocyclic group containing at 1 ast one nitrogen atom.

6. A compound according to claim 5 or a salt thereof, wherein the 5- to 7-membered nonaromatic heterocyclic group for the optionally substituted 5- to 7-membered nonaromatic heterocyclic group is pyrrolidine, imidazolidine, thiazolidine, isothiazolidine, oxazolidine, oxadiazolidine, piperidine, piperazine, thiomorpholine or morpholine.

7. A compound according to claim 1 or a salt thereof, wherein the optionally substituted nonaromatic heterocyclic group represented by R^1 has 1 to 4 substituents selected from among halogen, hydroxy, oxo, C_{1-10} alkyl, C_{1-6} alkoxy, C_{1-6} acyl, amino, mono- or di- C_{1-6} alkylamino, C_{1-6} alkylsulfonyl, carboxy, C_{1-6} alkoxy-carbonyl and phosphono groups.

8. A compound according to claim 3 or a salt thereof, wherein R^2 is hydrogen and R^4 is hydroxyl.

9. A compound according to claim 3 or a salt thereof, wherein R^2 and R^4 are both hydrogen.

10. A prodrug of a compound according to claim 1.

11. N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,4-dioxooxazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

5,7-dihydroxy-N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,4-dioxothiazolidin-5-yl)methyl]phenyl]-5-hydroxy-7-methoxy-4-oxo-4H-1-benzopyran-2-carboxamide,

5,7-dihydroxy-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

5-hydroxy-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-

benzopyran-2-carboxamide,

N-[4-[(2-oxazolidon-3-yl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

N-[4-[(2,6-dioxo-1-piperidinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide,

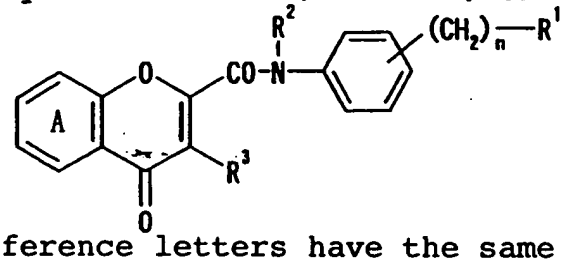
N-[4-[(2,4-dioxooxazolidin-5-yl)methyl]phenyl]-5-hydroxy-4-oxo-4H-1-benzopyran-2-carboxamide,

5-hydroxy-N-methyl-N-[4-[(4-morpholinyl)methyl]phenyl]-4-oxo-4H-1-benzopyran-2-carboxamide, or

4-oxo-N-[4-[(4-oxo-1-piperidinyl)methyl]phenyl]-4H-1-benzopyran-2-carboxamide,

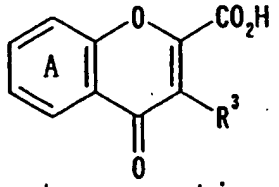
or a salt thereof.

12. A process for preparation of a chromone derivative represented by the following formula, or a salt thereof:

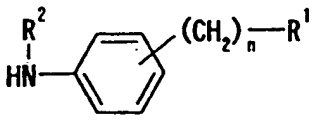


where the reference letters have the same definitions explained above,

characterized by reacting a compound represented by the following formula, a derivative thereof reactive at the carboxyl group, or a salt thereof:



where ring A represents an optionally substituted benzene ring and R^3 represents a hydrogen atom, hydrocarbon group or halogen, with a compound represented by the following formula, a derivative thereof reactive at the amino group, or a salt thereof:

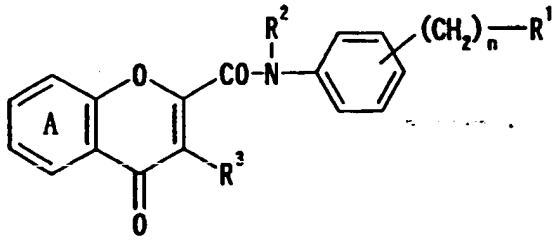


where R^1 represents an optionally substituted nonaromatic

heterocyclic group, R^2 represents a hydrogen atom or hydrocarbon group and n is an integer of 0 to 3.

13. 5,6-methylenedioxy-4-oxo-4H-1-benzopyran-2-carboxylic acid, 5,6-dihydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid or 5-hydroxy-7-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid, or a salt thereof.

14. A pharmaceutical composition comprising a chromone derivative represented by the following formula, or a salt thereof:



where ring A represents an optionally substituted benzene ring, R^1 represents an optionally substituted nonaromatic heterocyclic group, R^2 represents a hydrogen atom or hydrocarbon group, R^3 represents a hydrogen atom, hydrocarbon group or halogen, and n is an integer of 0 to 3.

15. A pharmaceutical composition according to claim 14, which is an osteogenesis accelerator.

16. A pharmaceutical composition according to claim 14, which is a prophylactic or treatment agent for bone disease.

17. A pharmaceutical composition according to claim 14, which is a prophylactic or treatment agent for bone fracture.

18. A pharmaceutical composition according to claim 14, which is a prophylactic or treatment agent for cartilage diseases.

19. A pharmaceutical composition comprising a prodrug according to claim 10.

20. An osteogenesis accelerating method characterized by administering a compound according to claim 1 or a salt thereof.

21. The use of a compound according to claim 1 or a salt thereof for preparation of an osteogenesis accelerator.